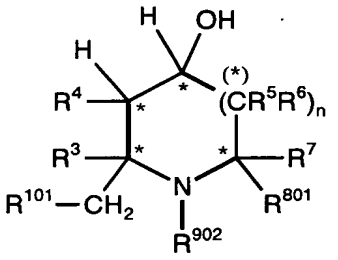
reacting a compound corresponding to formula Xa or a compound produced by cleaving off the silyl protecting group R11 with samarium (II) iodide for the reductive cleavage of the sulfonimidoyl-alkyl bond, in order to obtain a compound corresponding to formula Ib:



Ib

wherein

R^{101}, R^3, R^4, R^5, R^6, R^7, R^{801}, R^{902} and n have the above meanings,

and

optionally cleaving off any protecting groups in compounds of Formula Ia,

and

optionally reacting the optionally released NH group in the 1-position of the cyclic parent structure with a reagent capable of N-alkylation or a reagent capable of amide formation or blocking the released NH group with an amino protecting group,

thereby obtaining said compound corresponding to Formula Ia'.

20. (Amended) A process according to claim 17, wherein said base-labile amino protecting group is a fluoren-9-yl-methyloxy-carbonyl radical.

REMARKS

Favorable consideration and allowance are respectfully requested for claims 17, 18, 20-22, 24, 25, 27-29, and 31-33 in view of the foregoing amendments and the following remarks.

In the Office Action dated July 12, 2002, claim 27 was rejected under 35 U.S.C. § 102(a) as being anticipated by the Bolte article ("Bolte"); claims 27-28

were rejected under 35 U.S.C. § 103(a) as being unpatentable over Bolte in view of the Greene article ("Greene"); claims 17-25, and 31-33 were rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent No. 5,252,747 ("Chu"), Reggelin (Liebigs Ann./Receueil, 1997) ("Reggelin I"), Reggelin (J. Am. Chem. Soc., 1996) ("Reggelin II"), and Bolte in view of Greene. These rejections are respectfully traversed.

Claims 17 and 20 have been modified by this amendment, claims 19 and 23 are now cancelled, claims 1-16, 26, and 30 have been cancelled previously; thus, claims 17, 18, 20-22, 24, 25, 27-29, and 31-33 remain pending in this application.

Rejection under 35 U.S.C. § 102(a)

Claim 27 was rejected under 35 U.S.C. §102(a) as anticipated by Bolte. As set forth in the Amendment filed May 14, 2002, the disclosure of Bolte is insufficient to form an anticipatory disclosure. Bolte provides the structural formula of a compound, but no way to make the compound; as such, the rejection under 35 U.S.C. §102(a) is improper and should be withdrawn.

In the Office Action, the Examiner now alleges that the rejection applying the "non-enabling" Bolte article is proper because "the process of making the compound is well known in the art as described for the analogous tetrahydrofurans" and relies upon Reggelin I for support. See Office Action at 2.

The disclosure of Regglein I does not overcome the deficient disclosure of the Bolte article. Reggelin I describes the preparation of sulfoximine oxacyclics by the fluoride ion induced cyclization of isomerically pure 5-silyloxy-substituted vinyl sulfoximines. See, e.g., Reggelin I, page 1881, section "Results and Discussion," first paragraph. The fluoride-induced cyclization is a central feature of the Reggelin I publication and is necessary for the preparation of the oxacyclics. No other methods of cyclization are disclosed in Reggelin I. In contrast thereto, the intermediate products of the general formula Xa of claim 27 of the invention are not obtained by fluoride-induced cyclization of the corresponding precursor compounds of the formula IX. Instead, it is necessary in compounds of formula IX to split off a base-labile protective group R^{13} by means of a base, in order to achieve the desired cyclization to compounds of the formula Xa, which is not taught by Bolte. To emphasize this difference claim 17 has been modified to include the limitations of claim 19. It is respectfully submitted that claim 27 is not anticipated by Bolte; and, as such, it is requested that the rejection of claim 27 be withdrawn.

Rejection of claims 27-28 under 35 U.S.C. § 103(a)

Claims 27-28 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Bolte in view of Greene. For the reasons set forth above, Bolte does not set forth an enabling disclosure, and the method set forth by Reggelin I is insufficient as well. Greene also fails to remedy the deficiency of the combination of Bolte and

Reggelin I. Accordingly, it is respectfully submitted that the rejection under 35 U.S.C. §103(a) is improper and should be withdrawn.

Rejection of claims 17-25 and 31-33 under 35 U.S.C. § 103(a)

Claims 17-25 and 31-33 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Chu, Reggelin I, Reggelin II, and Bolte in view of Greene. Contrary to the Examiner's statement, the Chu patent does not describe "a compound of instant formula Ia'" as recited in claim 17. The compounds cited by the Examiner, (VI) in column 1 and (9) in column 5, contain no definite stereochemistry; rather, they are instead racemic with regard to the center of asymmetry. To produce a definite chemistry at asymmetry centers, Chu resorts to a conventional racemate cleavage. See Chu, diagram in columns 5 to 6 (from 12 to 12 (trans)), and corresponding text in column 6. However, the racemate cleavage process requires additional, strenuous process steps, which are unnecessary by the method of the invention according to claim 17. That is because the method of the invention permits the production of the compounds of formula Ia' in a single "one-pot process." The claimed invention accomplishes this result with a definite stereochemistry at several asymmetry centers, particularly for highly substituted pyrrolidines and piperidines wherein the substituent R^1R^2CH- in position 5 of the ring structure and the hydroxy group in position 3 on the ring structure are each in the trans position relative to eachother. Such is not taught or suggested by Chu or any of the secondary references.

As set forth in the Amendment filed May 14, 2002, Reggelin I teaches the synthesis of sulfoximide-substituted tetrahydrofurans, which are not claimed in the present invention. Reggelin I does not teach how to split off the sulfoximide auxiliaries from the systhesized furans, nor does the reference suggest that this might be useful. Further, Reggelin I does not suggest that the disclosed synthesis method could be extrapolated from aza pentacyclic compounds to aza hexacyclic compounds or bicyclic, tricyclic or tetracyclic ring systems of defined stereochemistry. As such, Reggelin I does not cure the deficiencies of Chu.

As discussed in the May 14th Amendment, the splitting method of Reggelin II always yields vinyl-substituted oxacyclic compounds that can be obtained only in positions 4 and 5 of the oxacyclic ring structure. Thus, Reggelin II does not disclose synthesis of free hetero cyclic compounds without a vinyl substituent. The present invention does not claim vinyl-substituted products; rather, the claimed invention is directed to aza cyclic compounds with methyl substitutions. More particularly, the invention, according to claim 17, recites a method for splitting off the sulfoximine auxiliary by employing samarium (II) iodide according to process step c). As such, no vinyl substituents in position 5 of the azacyclic ring structure are obtained. Instead, by the method of the invention, substituents saturated only at the desired place are obtained in position 5 of the azacyclic ring structure. To emphasize this point, the limitations of claim 23 have been incorporated into claim 17.

Bolte, as discussed above, fails to present a method for synthesis of the disclosed compound. Further, there is no disclosure that the compound is related to

a method of stereoselective synthesis of highly substituted aza cyclic compounds. The secondary references do not cure the deficiencies of Chu.

Greene discloses general background information for protective group chemistry, however, the fluoren-9-yl-methoxy-carbonyl (= FMOC) protective group is proposed only as one among numberless examples of possible nitrogen protective groups, without any reference to the subject of the present invention. Moreover, one of ordinary skill in the art, at the time the invention was made, would not be able, given the information on the mere existence of the FMOC nitrogen protective group, to predict that this protective group would have been especially advantageous for the process of the claimed invention. The motivation supporting this combination of references is only found in instant specification, not in the references themselves or in the knowledge of the art. In view of the large number of protective groups, it is not clear how the disclosure of some or all the groups claimed would render the chosen combination obvious. Further, assuming arguendo, even if the protective groups of Greene could be relied upon, the other cited references, whether taken singly or in combination, fail to set forth the claimed formula and method for making the same. Accordingly, withdrawal of the rejection of claims 17-25 and 31-33 is respectfully requested.

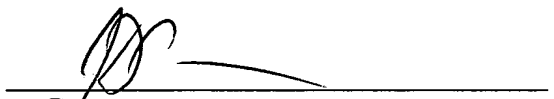
In view of the foregoing amendments and remarks, the application is respectfully submitted to be in condition for allowance, and prompt favorable action thereon is earnestly solicited.

If there are any questions regarding this amendment or the application in general, a telephone call to the undersigned would be appreciated since this should expedite the prosecution of the application for all concerned.

If necessary to effect a timely response, this paper should be considered as a petition for an Extension of Time sufficient to effect a timely response; please charge any deficiency in fees or credit any overpayments to Deposit Account No. 05-1323 (Docket #147/49227).

Respectfully submitted,

October 11, 2002



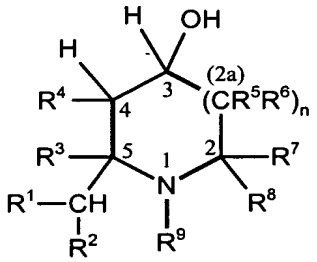
J. D. Evans
Registration No. 26,269
W. Jackson Matney, Jr.
Registration No. 39,292

CROWELL & MORING LLP
P.O. Box 14300
Washington, DC 20044-4300
Telephone No.: (202) 624-2500
Facsimile No.: (202) 628-8844

MARKED-UP VERSION TO SHOW CHANGES

IN THE CLAIMS

17. (Amended twice) A process for stereochemically controlled production of a compound corresponding to formula Ia':



Ia'

wherein the R^1R^2CH group in the 5-position of the cyclic parent structure and the hydroxy group in the 3-position of the cyclic parent structure are each in the trans position relative to each other and wherein the substituent R^4 in the 4-position and the hydroxy group in the 3-position of the cyclic parent structure are each in the cis position relative to each other, and wherein

n is 0 or 1,

R^1 is hydrogen;

R^2 is hydrogen;

R^3 is hydrogen, and

R^4 is hydrogen or lower alkyl, or

R^3 and R^4 also together are a C_3-C_6-alkylene chain optionally containing 1 to 3 double bonds or together form the 7, 7-dimethylbicyclo[3.1.1] heptyl-system

R^5 is hydrogen or lower alkyl, and

R^6 is hydrogen, and

R^7 is hydrogen, and

R^8 is hydrogen;

a monocyclic or bicyclic ring system selected from the group consisting of cyclopropyl, cyclopentyl cyclohexyl, phenyl, p-bromophenyl and 3-indolyl;

lower alkyl; phenyl-lower alkyl or lower-alkoxy lower alkyl, or

R^6 and R^7 also together may form a bond, and

R^5 and R^8, together with the carbon atoms to which they are bonded, may form an aromatic C_6-ring system,

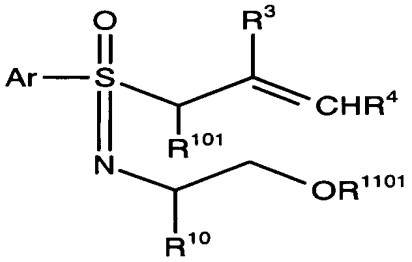
R^9 is hydrogen; lower alkyl; phenyl-lower alkyl optionally substituted one to three times in the phenyl ring by lower alkyl, lower haloalkyl, lower alkoxy or lower haloalkoxy; or an amino protecting group, or

R^8 and R^9 also together may form a C_3-C_4-alkylene chain,

or an acid addition salt thereof, wherein any reactive groups which may be present in said compound of Formula Ia' may be blocked by suitable protecting groups,

said process comprising the steps of:

a) reacting a compound corresponding to formula II:



II

wherein

R^3 and R^4 have the above meanings,

R^{101} has the meaning given above for R^1

Ar represents phenyl optionally substituted one to three times by lower alkyl,

R^{10} is lower alkyl, or phenyl optionally substituted once in the phenyl ring by lower alkyl or by hydroxy protected with a suitable protecting group, or phenyl-lower alkyl optionally substituted once in the phenyl ring by lower alkyl, and

R^{1101} stands for a silyl protecting group,

successively with

(i) a base for the deprotonation thereof,

(ii) an organometallic reagent corresponding to the formula VII:

VII

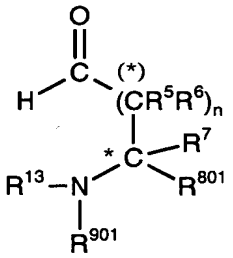
wherein

X is halogen,

M^2 is a tetravalent transition metal, and

R^{12} is lower alkyl, phenyl or phenyl-lower alkyl, and

(iii) a stereoisomer of a compound of the general formula VIII:



VIII

wherein

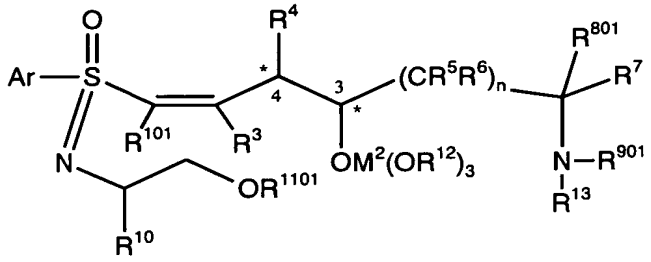
R^5, R^6, R^7 and n have the above meanings,

R^{801} has the meaning of R^8, with any reactive groups, if necessary, being blocked by base-stable protecting groups,

R^{901} is hydrogen or together with R^{801} forms a C_3-C_4-alkylene chain, and

R^{13} is [an] a base-labile amino protecting group which when cleaved leaves behind a nitrogen nucleophile,

to form a stereoisomer of a compound corresponding to the formula IX:



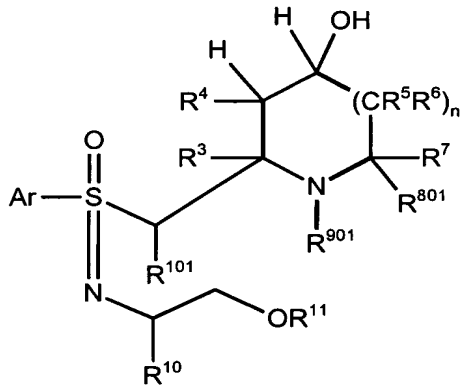
IX

wherein

R^{101}, R^3, R^4, R5, R^6, R^7, R^{801}, R^{901}, R^{10}, R^{1101}, R^{12}, R^{13}, n, Ar and M2 have the above meanings,

and

c) converting the compound of Formula IX by treatment with a base reagent for removing the group R^{13}, into a compound corresponding to formula Xa:



Xa

wherein

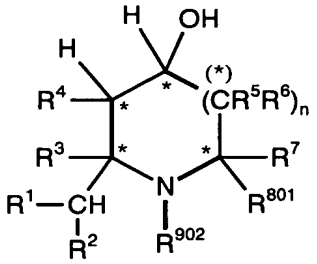
R^{101}, R^3, R^4, R^5, R^6, R^7, R^{801}, R^{901}, R^{10}, n and Ar have the above meanings, and R^{11} is hydrogen or a silyl protecting group,

and

if R^{901} is hydrogen, blocking the nitrogen atom in the cyclic parent structure of the resulting compound of Formula Xa with a base-stable protecting group, and cleaving off any silyl protecting group R^{11} which may still be present;

and

c) for the production of a compound corresponding to formula Ia:



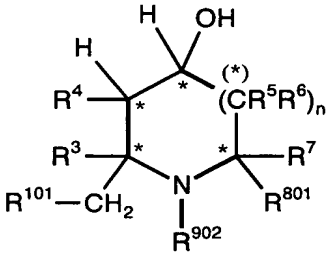
Ia

wherein

R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^{801} and n have the above meanings, and

R^{902} stands for a base-stable protecting group or, together with R^{801}, for a C_3-C_4-alkylene chain,

reacting a compound corresponding to formula Xa or a compound produced by cleaving off the silyl protecting group R11 with [a reagent] samarium (II) iodide for the reductive cleavage of the sulfonimidoyl-alkyl bond, in order to obtain a compound corresponding to formula Ib:



Ib

wherein

R^{101}, R^3, R^4, R^5, R^6, R^7, R^{801}, R^{902} and n have the above meanings,

and

optionally cleaving off any protecting groups in compounds of Formula Ia,

and

optionally reacting the optionally released NH group in the 1-position of the cyclic parent structure with a reagent capable of N-alkylation or a reagent capable of amide formation or blocking the released NH group with an amino protecting group,

thereby obtaining said compound corresponding to Formula Ia'.

20. (Amended) A process according to claim [19] 17, wherein said base-labile amino protecting group is a fluoren-9-yl-methyloxy-carbonyl radical.